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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,621	TAYLOR ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 18,19,21,22,24-27 and 32-62 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 18,19,21,22,24-27 and 32-53 is/are rejected.

7)☐ Claim(s) 54-62 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date Sep 15, 2005.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 20, 23 and 28-31 have been canceled. Claims 18, 19, 21, 22, 32, , 39-44, 46-50 have been amended. Claims 51-62 have been added. Claims 18, 19, 21, 22, 24-27, 32-62 are pending and under consideration.

2. Sections of Title 35, U.S. Code not found in this action can be found in a prior action.

3. The rejection of claims 18, 19, 38, 39, 40, 42, 46 and 48 under 35 U.S.C. 103(a) as being unpatentable over Taylor et al (US 5,470,570) in view of the abstract of Stoiber et al (Immunobiology, 1995, Vol. 193, pp. 98-113) is maintained for reasons of record.

Claim 18 is drawn to a method for inhibiting viral replication in an animal, said method comprising administering to the animal a therapeutically effective amount of one or more ani-C3b(i) antibodies.

Claim 19 is drawn to a method for inhibiting viral replication in an animal, said method comprising administering to the animal a therapeutically effective amount of one or more ani-C3b(i) antibodies and one or more antibodies specific to one or more viral antigens.

Claim 38 embodies the methods of claims 18 or 19 in which at least one of the antibodies is conjugated to a therapeutic agent.

Claims 39 and 40 embody the methods of claims 18 and 19, wherein the animal is a mammal and a human, respectively.

Claim 42 embodies the method of claims 18 or 19 wherein at least one of the anti-C3b(i) antibodies is immunospecific for C3b(i) linked to a viral antigen. Claim 46 specifies that the viral antigen of claim 42 is gp120 of HIV. Claim 48 embodies the method of claim 18 or 19 wherein the viral infection is caused by a retrovirus.

Taylor et al teach a method of using franked red blood cells with specificity to an antigen such as HIV to clear free antigen from the blood of a human patient (column 7, lines 1-3), and a method of using franked red blood cells with specificity to C3b (column 7, lines 7-8). Taylor et al teach that the level of free HIV in the blood is the most cytopathic form of the virus (column 7, lines 55-58). It is noted that the specification defines C3b(i) as including C3b and its fragments such as C3bi, C3b and C3d (page 7, lines 6-7) and antibodies which bind to C3b(i) as

antibodies which bind to C3b-opsonized cells (page 7, lines 11-12). Taylor et al teach that RBCs can be franked with a cocktail of several heteropolymers which in addition to the binding of target antigen, can also bind to non-overlapping epitopes of CR1 which allows a small number of RBC to bind a larger number of antigen (column 2, lines 41-56). Taylor et al do not specifically teach franked red blood cells with cocktails of heteropolymers specific to both an HIV antigen and C3b on target HIV.

The abstract of Stoiber et al teaches that C3b reacts with the gp120 envelope protein of HIV-1 (abstract).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to frank red blood cells with a cocktail of heteropolymers which comprised anti-CR1 antibodies which bound to different epitopes of CR1, conjugated to anti-C3b antibodies, and anti-C3b antibodies which bind to C3b attached to gp120 and to administer said franked red blood cells for the treatment of HIV infection, and it would have been an intrinsic property that the antibody would bind to C3b attached to gp120, because The abstract of Stoiber teaches that C3b reacts with gp120. One of skill in the art would have been motivated to do so by the teachings of The abstract of Stoiber et al on the deposition of C3b on HIV-1 and the specific interaction of C3b with gp120. The franked red blood cells would fulfill the specific embodiments of claim 38 because the therapeutic agent would be the erythrocyte.

4. The rejection of claims 18, 19, 34, 38, 39, 40-42, 46 and 48 under 35 U.S.C. 103(a) as being unpatentable over Taylor et al and the abstract of Stoiber et al as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48 above, and further in view of Nilsson et al (Molecular Immunology, 1987, vol. 24, pp. 487-494) is maintained for reasons of record. New claim 62 is also rejected for the same reasons of record.

Claim 34 specifies that the methods of claims 18 and 19, wherein at least one of the anti-C3b(i) antibodies is a monoclonal antibody.

Claim 41 embodies the method of claims 18 or 19 wherein at least one of the antibodies is immunospecific for C3bi linked to IgM or IgG antibody bound to a virus.

Neilsson et al teach monoclonal anti-C3(D) antibodies which bind exclusively to neoantigenic epitopes found in physiologically bound C3 and are thus reagents for the detection

of immune complex bound C3b and iC3b (Table 3 and page 493, second column, lines 13-16 and lines 35-39).

It would have been prima facie obvious at the time the invention was made to use the use the monoclonal anti-C3(d) antibodies as taught by Neilsson et al as part of the heteropolymer rendered obvious by the combination of Taylor et al and the abstract of Stoiber et al. One of skill in the art would have been motivated to do so by the teachings of Neilsson et al on the ability of said anti-C3(D) antibodies to bind to physiologically bound forms of C3. One of skill in the art would have been motivated to include such an antibody in order to eliminate binding to C3 or C3 fragments which were not physiologically bound to the HIV virus.

5. The rejection of claims 18, 19, 34, 35, 38, 39, 40-42, 46 and 48 under 35 U.S.C. 103(a) as being unpatentable over Taylor et al, the abstract of Stoiber et al and Nilsson et al as applied to claims 18, 19, 34, 38, 39, 40-42, 46 and 48 above, and further in view of Queen et al (5,530,101) is maintained for reasons of record.

Claim 35 embodies the monoclonal antibody of claim 34 which is human or humanized.

Taylor et al teach that available human monoclonal antibodies can be used to prepare the heteropolymers to avoid host immune response (column 7, lines 46-48). Nilsson et al teach a monoclonal antibody which specifically binds to C3 fragments physiologically bound to substrate. None of the combined references specifically teach a human or humanized anti-C3b antibody.

Queen et al teach that the immune response mounted by a patient against a non-human antibody can be quite strong, essentially eliminating the therapeutic effect of the antibody after an initial treatment (column 1,lines 41-47). Queen et al teach a method for making humanized antibodies specifically reactive with strong affinity to a predetermined antigen which remain substantially non-immunogenic in humans (column 2, lines 25-31).

It would have been prima facie obvious at the time the claimed invention was made to make the heteropolymer rendered obvious by the combination of Taylor et al and The abstract of Stoiber et al with a humanized anti-C3(D) antibody as taught by Nilsson et al. One of skill in the art would have been motivated to do so by the suggestion of Taylor et al that human antibodies

be utilized in the heteropolymer and the teachings of Queen et al on the humanization of antibodies to decrease their immunogenicity in vivo while retaining antigen affinity.

6. The rejections of claims 18, 19, 24-26, 34, 38, 39, 40, 42, 46 and 48 under 35 U.S.C. 103(a) as being unpatentable over Taylor et al (US 5,470,570) and the abstract of Stoiber et al (Immunobiology, 1995, Vol. 193, pp. 98-113) as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48 above, and further in view of Montefiori et al (Journal of Infectious Diseases, 1994, Vol. 170, pp. 429-430) is maintained for reasons of record.

Claims 24 and 25 embody the methods of claims 18 and 19 further comprising administering IgG enriched plasma and IgM enriched plasma. Claim 26 embodies the method of claim 24 further comprising administering IgM enriched plasma.

Montefiori et al teach that complement alone targeted HIV-1 to red blood cells but envelope specific antibodies increased this effect (abstract, lines 7-10). Montefiori et al teach that the envelope-specific antibodies were obtained from gp-160 immunized volunteers (page 431, second column, lines 6-8). It is reasonable to conclude that the sera from the vaccinated volunteers harbored both IgG and IgM anti-gp160 antibodies.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to administer envelope-specific antibodies in addition to the franked erythrocytes rendered obvious by the combination of Taylor et al and The abstract of Stoiber et al. One of skill in the art would have been motivated to do so by the teachings of Montefiori et al on the increase of binding to the CR1 receptor by opsonized envelope specific antibodies and complement. One of skill in the art would have been motivated to increase the binding of free HIV-1 to the CR1 receptor in order to target the free HIV-1 to the reticulo-endothelial system as taught by Taylor et al.

7. The rejection of claims 18, 19, 34, 38, 39, 40, 42, 46 and 48 under 35 U.S.C. 103(a) as being unpatentable over Taylor et al and the abstract of Stoiber et al as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48 above, and further in view of Peng et al (Clinical and Diagnostic Laboratory Immunology, 1996, Vol. 3, pp. 128-131) is maintained for reasons of record.

Claim 27 embodies the method of claims 18 and 19 further comprising administering one or more complement components.

The combination of Taylor et al and The abstract of Stoiber et al render obvious the limitations of claims 18, 19, 34, 39, 40, 42, 46 and 48 for the reasons set forth above. Neither of the references teaches the administration of one or more complement components.

Peng et al teaches that HIV infection leads to complement deficient immune complexes (page 130, second column, last paragraph).

It would have been prima facie obvious at the time the claimed invention was made to administer complement components in conjunction with the franked red blood cells rendered obvious by the combined teachings of Taylor et al and The abstract of Stoiber et al. One of skill in the art would be motivated to do so in order to provide adequate C3b deposition on free HIV-1, so that the heteropolymers comprising the anti-C3bi antibodies on the franked red blood cells will bind multiple HIV viruses.

8. The rejection of claims 18, 19, 33, 36-39, 40, 42, 46 and 48 under 35 U.S.C. 103(a) as being unpatentable over Taylor et al and the abstract of Stoiber et al as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48 above, and further in view of Lenz et al (US 6,060,285) is maintained for reasons of record.

Claim 33 is drawn to the method of claim 18 or 19 wherein at least one of the anti-C3b(i) antibodies is a bispecific antibody which binds to C3b(i) and a effector cell receptor or antigen. Claim 36 embodies in part the method of claim 33 wherein the effector cell is a erythrocyte. Claim 37 embodies in part the method of claim 33 wherein the antigen is CR1.

The combination of Taylor et al and The abstract of Stoiber et al render obvious the instant claims wherein the heteropolymer consists of anti-CR1 antibodies which bind to non-overlapping epitopes of CR1 conjugated to anti-C3b antibodies for the reasons set forth above. Neither Taylor et al nor The abstract of Stoiber et al teach bi-specific antibodies which bind CR1 and C3b.

Lenz et al teach bispecific antibodies which have two different antigen binding sites directed towards two different epitopes useful for the therapy of diseases. Lenz et al teach an example of a bispecific antibody having one antigen binding site directed towards a T-cell

surface antigen and the second antigen binding site is directed towards an antigenic determinant of a virus column 1, lines 7-18). Lenz et al teach that the bi-specific antibodies are especially suitable for diseases caused by viruses and that the therapist has a wide field from which he can choose the respective best combination of the two antigenic determinants (column 4, lines 5-9). Lenz et al teach a method for making the bi-specific antibodies which is less complicated than a method of chemically conjugating two different antibodies (column 1, lines 21-27), such as that used for the production of the heteropolymer taught by Taylor et al.

It would have been prima facie obvious at the time the claimed invention was made to substitute bi-specific antibodies which bind to both the CR1 receptor of a red blood cell and C3b on the target HIV-1 viron in the method rendered obvious by the combination of Taylor et al and The abstract of Stoiber et al. One of skill in the art would have been motivated to do so by the teachings of Lenz et al on the ease of making such bi-specific antibodies relative to chemically conjugating two different antibodies and the high yield of bi-specific antibodies attained through the method of Lenz et al.

9. Applicant argues that neither Taylor nor Stoiber alone or in combination teach or suggest the methods recited in the pending claims. Applicant contends that Taylor teaches heteropolymers comprising a monoclonal antibody specific to CR1 combined with monoclonal antibodies specific to an antigen to chemically attach the homopolymer to the erythrocyte, and the use of such franked erythrocytes for the neutralization and/or clearance of antigens or immunogens from the circulatory system. Applicant further argues that Taylor does not teach or suggest a method of inhibiting or suppressing viral replication in an animal comprising administering an anti-C3b(i) antibody. Applicant argues that the further references combined with Taylor and Stoiber do not make up for the deficiencies of Taylor and Stoiber. This has been considered but not found persuasive. Taylor does indeed suggest the use of franked erythrocytes for the removal of free HIV virus from the circulation which amounts to the inhibition and suppression of viral replication in an animal.

10. The rejection of claims 18, 24, 34, 38, 39, 40 and 48 under 35 U.S.C. 103(a) as being unpatentable over Taylor et al (US 5,470,570) in view of Ebenbichler et al (Journal of

Experimental Medicine, 1991, Vol. 174, pp. 1417-1424) and Nilsson et al (Molecular Immunology, 1987, vol. 24, pp. 487-494) is maintained for reasons of record.

Taylor et al teach a method of using a franked red blood cells with specificity to an antigen such as HIV to clear free antigen from the blood of a human patient (column 7, lines 1-3), and a method of using franked red blood cells with specificity to C3b (column 7, lines 7-8). Taylor et al teach that the level of free HIV in the blood is the most cyopathic form of the virus (column 7, lines 55-58). It is noted that the specification defines C3b(i) as including C3b and its fragments such as C3bi, C3b and C3d (page 7, lines 6-7) and antibodies which bind to C3b(i) as antibodies which bind to C3b-opsonized cells (page 7, lines 11-12). Taylor et al teach that RBCs can be franked with a cocktail of several heteropolymers which in addition to the binding of target antigen, can also bind to non-overlapping epitopes of CR1 which allows a small number of RBC to bind a larger number of antigen (column 2, lines 41-56). Taylor et al do not specifically teach franked red blood cells with cocktails of heteropolymers specific to both an HIV antigen and C3b on target HIV.

Ebenbichler et al teach that retroviruses isolated from avian, feline, murine and simian sources direct the induction of the classical complement pathway, whereas cells infected with said retroviruses activate the alternative pathway (page 1417, first column, lines 1-4 and lines 11-15). Ebenbichler et al teach the deposition of C3b and C3d on HIV infected cells (page 1417, first column, lines 13-14).

Neilsson et al teach monoclonal anti-C3 antibodies (D) which bind exclusively to neoantigenic epitopes found in physiologically bound C3 and are thus reagents for the detection of immune complex bound C3b and iC3b (Table 3 and page 493, second column, lines 13-16 and lines 35-39).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to frank red blood cells with a cocktail of heteropolymers which comprised anti-CR1 antibodies which bound to different epitopes of CR1, wherein said anti-CR1 antibodies are conjugated to the anti-C3(D) antibody taught by Neilsson et al and to administer said franked red blood cells for the treatment of retrovirus infections. One of skill in the art would have been motivated to do so by the teachings of Ebenbichler et al on the activation of complement by both free retroviruses and retrovirus-infected cells and the deposition of C3 onto retrovirus infected

cells. One of skill in the art would recognize that the C3b and/or the C3bi would be specific to a retrovirus-infected cell versus a non-retrovirus infected cells and therefore C3b or C3bi can be used as a target antigen for said cells.

11. The rejection of claims18, 24, 33, 34, 36-40 and 48 under 35 U.S.C. 103(a) as being unpatentable over Taylor et al and Ebenbichler et al and Nilsson et al as applied to claims 18, 24, 34, 38, 39, 40 and 48 above, and further in view of Lenz et al (US 6,060,285) is maintained for reasons of record.

Claim 33 embodies the method of claim 18 wherein at least one of the anti-C3bi antibodies is a bispecific antibody which is immunospecific for C3bi and an effector cell antigen. Claim 36 embodies the method of claim 33 in which the effector cell is a monocyte, macrophage, dendritic cell, neutrophil, natural killer cell or erythrocyte. Claim 37 embodies the method of claim 33 in which the antigen is CR1, CR2, CR3, CR4, CD16, CD32, CD64 or CD89.

The combination of Taylor et al and Ebenbichler et al render obvious the instant claims wherein the heteropolymer consists of anti-CR1 antibodies which bind to non-overlapping epitopes of CR1 conjugated to anti-C3(D) antibodies for the reasons set forth above. Neither Taylor et al nor Ebenbichler et al teach bi-specific antibodies which bind CR1 and C3(D).

Lenz et al teach bispecific antibodies which have two different antigen binding sites directed towards two different epitopes useful for the therapy of diseases. Lenz et al teach an example of a bispecific antibody having one antigen binding site directed towards a T-cell surface antigen and the second antigen binding site is directed towards an antigenic determinant of a virus column 1, lines 7-18). Lenz et al teach that the bi-specific antibodies are especially suitable for diseases caused by viruses and that the therapist has a wide field from which he can choose the respective best combination of the two antigenic determinants (column 4, lines 5-9). Lenz et al teach a method for making the bi-specific antibodies which is less complicated than a method of chemically conjugating two different antibodies (column 1, lines 21-27), such as that used for the production of the heteropolymer taught by Taylor et al.

It would have been prima facie obvious at the time the claimed invention was made to substitute bi-specific antibodies which bind to both the CR1 receptor of a red blood cell and C3(D) on the target free retroviruses or cells infected with retroviruses in the method rendered

obvious by the combination of Taylor et al and Ebenbichler et al. One of skill in the art would have been motivated to do so by the teachings of Lenz et al on the ease of making such bi-specific antibodies relative to chemically conjugating two different antibodies and the high yield of bi-specific antibodies attained through the method of Lenz et al.

12. Applicant argues that the deficiencies in the teachings of Taylor et al are not cured by Ebenbichler and Nilsson, because Nilsson describes the production of murine monoclonal antibodies that bind to distinct neoantigen epitope on bound C3b and C3b(i), and Ebenbichler describes a direct interaction between C1 complex and HIV and suggests that said interaction results in the enhancement of HIV-1 infection. This has been considered but not found persuasive. The teachings of Nilsson indicate that bound C3b or C3bi can be used as a target antigen for cells infected with retrovirus by using the described antibodies which selectively bind to bound C3b or bound C3b(i) rather than free C3b. Echenbichler teaches that C3b is deposited on cells infected with HIV, Thus it would be obvious to one of skill in the art that these teachings set forth bound C3b or bound C3b(i) as a target antigen on a pathogen, or pathogen-infected cell which can specifically bind to the antibodies of Nilsson.

13. The rejection of claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 under 35 U.S.C. 103(a) as being unpatentable over Fanger et al (EP 255, 249) as evidenced by Abbas et al (Cellular and Molecular Immunology (text), 1991, pp. 398-400) in view of Newman et al (Journal of Experimental Medicine, 1985, Vol. 161, pp. 1414-1431) and Neilsson et al (Molecular Immunology, 1987, vol. 24, pp. 487-494) as evidenced by Vogel et al (Infections and Immunity, 1997, Vol. 65, pp. 4022-4029) is maintained for reasons of record.

Claim 21 is drawn to a method for inhibiting microbial replication in an animal, said method comprising administering to the animal a therapeutically effective amount of one or more ani-C3b(i) antibodies. Claim 33 embodies the method of claims 21 wherein at least one of the anti-C3bi antibodies is a bispecific antibody which is immunospecific for C3bi and an effector cell receptor antigen. Claim 34 embodies the method of claims 21 wherein at least one of the C3bi antibodies is a monoclonal antibody. Claim 36 embodies the methods of claims 33 wherein the effector cell is a lymphocyte, monocyte, macrophage, dendritic cell, neutrophil,

natural killer or erythrocyte. Claim 37 embodies the method of claim 33 in which the antigen is CR1, CR2, CR3, CR4, CD16, CD32, CD64 or CD89. Claim 38 embodies the methods of claim 21 or 32 in which at least one of the C3bi antibodies is conjugated to a therapeutic agent. Claims 39 and 40 embody the method of claim 20, wherein the animal is a mammal and a human, respectively. Claim 43 embodies the methods of claim 21 wherein at least one of the anti-C3bi antibodies is immunospecific for C3bi linked to IgM or IgG bound to a microbe. Claim 44 embodies the method of claim of claim 21 wherein at least one of the anti-C3bi antibodies is immunospecific for C3bi linked to a microbial antigen. Claim 47 embodies the method of claim 44 in which at least one of the microbial antigens is LPS. Claim 49 embodies the methods of claim 21 in which the microbial infection is a bacterial infection. Claim 50 embodies the method of claim 49 wherein the bacterial infection is caused by S pyrogenes, S pnemoniae, H influenza, S aureus and E coli.

Fanger et al teach a method for eliminating undesirable target cells which include microorganisms such as bacteria and viruses comprising administering a bi-specific antibody which binds to the Fc receptors of effector cells (abstract, lines 8-11, page 5, lines 49-50 and page 8, lines 49-50). Fanger et al teach that the target cell can be a cancer cell or other cell whose elimination would be beneficial to the host, wherein target cell specificity of the bifunctional antibody or the hetero-antibody is derived from a targeting antibody i.e., an antibody specific for a target cell-associated or target cell-specific antigen (page 3, lines 29-32). Fanger et al teach bifunctional antibodies or heteroantibodies for the targeting of effector cells in which the antibodies have dual antigen binding specificity -one specificity for the Fc receptor and one specificity for an epitope of the target cell (page 5, lines 8-10). The teachings of Fanger et al fulfill the specific embodiments of claim 37 because the Fc receptors on the surface of macrophage and monocytes are gamma, I, II and III, which are the same as CD64, CD32 and CD16, respectively, as evidenced by the "Common Synonyms" provided by the appendix of Abbas et al. Fanger et al teach that the Fc receptor specificity mediates linkage to the effector cell through a known cytotoxic trigger molecule and that the target cell specificity provides for recognition and binding to the target cell (page 5, lines 10-12). Fanger et al teach that the use of the Fc specific antibody of this invention provides for attachment of the targeting antibody to monocyte effector cells by a linkage which is not disrupted by physiological levels of

immunoglobulin G encountered in vivo allowing for the administration of the targeted effector cells without loss of effector cell specificity due to IgG competition for Fc receptor sites (page 3, lines 32-37). Fanger et al teach that the antibody binds the high affinity (p72) Fc receptor (FcRI) for human IgG without being blocked by human IgG and that preferred anti-FcRI receptor antibody has the following characteristics: a. the antibody reacts specifically with the high affinity Fc receptor; b. the antibody reacts with the receptor through its antigen combining region independent of its Fc portion; c. the antibody reacts with an epitope of FcRI which is distinct from the Fc (or ligand binding) site of the receptor; and d. the antibody binds ligand (Fc) occupied receptor (page 4, lines 9-16). Fanger et al teach that effector cells for targeting include human leukocytes, preferably macrophages and monocytes, IFN-gamma activated neutrophils, and possibly IFN-gamma activated natural killer (NK) cells and eosinophils (page 5, lines 52-55). Fanger et al does not teach bi-specific antibodies which target C3 or C3bi on bacteria.

Newman et al teach that E coli, S pnemoniae, S pyrogenes, S aureus and H influenza all activate the alternative complement pathway and require phagocytosis for removal from the host. Newman et al teach that when the aforesaid bacteria were incubated in serum, between 16-28% of the C3b was converted to C3bi (page 1426, lines 1-6 of the third paragraph). Thus, S pnemoniae, S pyrogenes, S aureus and H influenza have a mixture of C3b and C3bi on their surfaces.

Neilsson et al teach monoclonal anti-C3 antibodies (D) which bind exclusively to neoantigenic epitopes found in physiologically bound C3 and are thus reagents for the detection of immune complex bound C3b and iC3b (Table 3 and page 493, second column, lines 13-16 and lines 35-39) and fulfill the specific embodiments of claims 43 and 44 because the physiologically bound C3b and C3bi to which the anti-C3(D) antibodies bind would include C3b and C3bi attached to a microbial antigen as well as C3b and C3bi attached to IgM on the surface of the bacterium. Neilsson et al fulfill the specific embodiments of claim 47 because the physiologically bound C3b and C3bi is linked to the surface structure of encapsulated bacteria which comprises LPS, as evidenced by Vogel et al (abstract, lines 7-9).

It would have been prima facie obvious at the time the invention was made to use the anti-C3 (D) antibodies of Neilsson et al in the method of eliminating bacteria as taught by Fanger et al. One of skill in the art would have been motivated to do so by the teachings of Newman et

al regarding the deposition of C3 b on the surface of E coli, S pnemoniae, S pyrogenes, S aureus and H influenza and the subsequent degradation of same of the C3b to C3bi, and the teachings of Neilsson et al on the anti-C3(D) antibodies which bind to both physiologically bound C3b and C3bi

14. The rejection of claims 21, 33, 34, 36-40, 43, 44, 47, 49, 50 under 35 U.S.C. 103(a) as being unpatentable over Fanger et al and Newman et al and Neilsson et al and Vogel et al as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 above, and further in view of and Todd (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1-2) and Fang et al (Journal of Immunology, 1998, Vol. 160, pp. 5273-5279) and Abbas et al (Cellular and Molecular Immunology, (text), 1991, page 273) and the abstract of Pulford et al (Int Immunol, 1990, Vol. 2, pp. 973-980) is maintained for reasons of record. New claims 51-53 are also rejected for the same reasons of record.

Claim 37 embodies the method of claim 33 in which the antigen is CR1, CR2, CR3, CR4, CD16, CD32, CD64 or CD89. Claim 51 is drawn to a method for inhibiting or suppressing viral replication in an animal in need thereof, said method comprising administering to said animal a therapeutically effective amount of a bi-specific antibody which is immunospecific for C3b(i) and an effector cell receptor or antigen. Claim 52 embodies the method of claim 51 wherein the effector cell is a lymphocyte, monocyte, macrophage, dendritic cell, neutrophil, NK cell or erythrocyte. Claim 53 embodies the method of claim 51 wherein the antigen is CR1, CR2, CR3, CR4, CD16, CD32, CD64 or CD90.

The combination of Fanger et al as evidence by Abbas et al and Newman et al and Neilsson et al render obvious the instant claims wherein the effector cell antigen to which the bispecific or heterospecific antibodies bind is CD16, CD32 and CD64 for the reasons set forth above. Fanger et al teach that effector cells for targeting include human leukocytes, preferably macrophages and monocytes, IFN-gamma activated neutrophils, and possibly IFN-gamma activated natural killer (NK) cells and eosinophils (page 5, lines 52-55). The combination does not specifically teach the effector cell antigens of CR4 or CD89.

Fang et al teach that CR1 is expressed on the surface of erythrocytes, macrophage, neutrophils, B-cells, follicular dendritic cells and a subset of T-cells (page 5273, second column.

lines 1-4). Fang et al teach that CR2 is expressed on the surface of follicular dendritic cells and some T-cells (page 5273, second column, lines 18-19).

Todd teaches that CR3 is expressed on the surface of mononuclear phagocytes and natural killer cells (page 1, column 2, lines 4-7).

Abbas et al identify CR4 as found on neutrophils and monocytes.

The abstract of Pulford et al teaches that CD68 is expressed by macrophage and monocytes.

It would have been prima facie obvious at the time the claimed invention was made to use the method rendered obvious by the combination of Fanger et al and Newman et al and Neilsson et al to target leukocytes, such as macrophages and monocytes, neutrophils, or natural killer (NK) cells by means of bispecific antibodies or heteroantibodies which bind CR1, CR2, CR3, CR4, or CD68. One of skill in the art would have been motivated to do so by the teachings of Fang et al, Todd, Abbas et al or the abstract of Pulford et al which identifies the aforesaid antigens as present on leukocytes and the suggestion by Fanger et al that the effector cells could be human leukocytes.

15. The rejection of claims 21 24-27, 33, 34, 36-40, 43, 44, 47, 49, 50 under 35 U.S.C. 103(a) as being unpatentable over Fanger et al and Abbas et al and Newman et al and Neilsson et al and Vogel et al as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 above, and further in view of Quie (Scand J Infect Dis, 1971, suppl. 31, pp. 34-40) is maintained for reasons of record.

Claim 24 embodies the method of claim 21 further comprising administering IgG enriched plasma. Claim 25 embodies the method of claim 21 further comprising administering IgM enriched plasma. Claim 26 embodies the method of claim 25 further comprising administering IgM enriched plasma. Claim 27 embodies the method of claim 21 further comprising administering one or more complement components.

The combination of Fanger et al as evidence by Abbas et al and Newman et al and Neilsson et al and Vogel et al render obvious the instant claims wherein the effector cell antigen to which the bispecific or heterospecific antibodies bind is CD16, CD32 and CD64 for the

reasons set forth above. None of the aforesaid references specifically teaches the administration of IgG or IgM enriched plasma.

Quie teaches that IgG antibodies on the surface of microbes are efficient opsonins acting by attachment of the antibody Fc region to the Fc receptors on phagocytic cells and that IgM antibodies are efficient activators of complement on the surface of microbes and act indirectly as opsonins by fixing C3b which can then attach to C3b receptors on phagocytic cells (page 38, first column, lines 27-33). Quie et al teaches that the alternative pathway of complement activation is critical for protection against septicemia as evidenced by the ability of virulent E coli, such as K-1 to resist activation of the alternative pathway and to result in the septic state (page 35, column 2, lines 13-19). Quie teaches that when specific antibodies are present, there is antibody mediated activation of the complement pathway via the classical pathway and C3b is deposited on the microbial surface in spite of the sialic acid on the E coli surface (page 35, second column, lines 31-36). Quie teaches that a clear separation between the classical pathway ad the alternative pathway is not possible because C3b activated by the classical pathway is part of C3b of the alternative pathway and both pathways may be antibody independent or antibody dependent. (35, second column, lines 37-43).

It would have been prima facie obvious at the time the claimed invention was made to further administer IgG enriched and IgM enriched plasma and C3b molecules in addition to the bispecific or heterospecific antibodies rendered obvious by the teachings of Fanger et al as evidenced by Abbas et al and Newman et al and Neilsson et al. One of skill in the art would have been motivated to provide IgG enriched plasma to increase the phagocytosis of the microbial cells according to the teachings of Quie. One of skill in the art would have been motivated to provide IgM enriched plasma to increase the deposition of C3b on the microbial cells to increase the opsonization of the microbial cells and to facilitate the binding of the bi-specific or heterospecific antibodies rendered obvious by Fanger et al as evidenced by Abbas et al and Newman et al and Neilsson et al

16. The rejection of claims 21, 22, 32, 33, 34, 36-40, 43-45, 47, 49, 50 under 35 U.S.C. 103(a) as being unpatentable over Fanger et al as evidenced by Abbas et al and Newman et al and Neilsson et al and Vogel et al as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49 and

50 above, and further in view of Seelen et al (Immunology, 1995, Vol. 84, pp. 653-661) is maintained for reasons of record.

Claim 22 is drawn to a method for inhibiting microbial replication in an animal, said method comprising administering to the animal a therapeutically effective amount of one or more ani-C3b(i) antibodies and one or more antibodies specific to one or more microbial antigens.

Claim 32 is drawn to a method of inhibiting septic shock in an animal comprising administering to said animal one or more anti-C3bi antibodies. Claim 45 embodies the method of claim 32 wherein at least one of the anti-C3bi antibodies is immunospecific for C3bi linked to LPS.

The combination of Fanger et al as evidence by Abbas et al and Newman et al and Neilsson et al and Vogel et al render obvious the instant claims for the clearance of bacteria from a patient by means of bispecific of heterospecific antibodies that bind to C3b or C3bi and an effector cell antigen for the reasons set forth above. The combination of references does not specifically address the treatment of sepsis or the administration of an antibody immunospecific for one or more microbial antigens.

Seelen et al teach the administration of the human IgM antibody, HA-1A, to patients with presumed gram-negative sepsis (page 653, second column, lines 5-8). Seelen et al teach that the anti-lipid A antibody binds to rough and smooth gram negative bacteria and that binding to the "rough" gram negative organism, S minnesota, enhanced classical pathway complement fixation, deposition of C3bi on the bacterial surface and mediated binding to erythrocyte CR1 and to monocytes (page 660, first column, lines 15-23). Seelen et al teach that complement fixation, delivery to the reticulo-endothelial system or direct enhancement of opsonization contributes to the clearance of certain bacteria in the septic patient. (page 660, first column, lines 27-33).
It would have been prima facie obvious at the time the claimed invention was made to treat sepsis by the method rendered obvious in the combination of Fanger et al as evidenced by Abbas et al and Newman et al and Neilsson et al and Vogel in addition to the administration of an anti-lipid A antibody. One of skill in the art would have been motivated to do so by the teachings of Seelen et al on the enhancement of C3 deposition by the anti-lipid A antibody, E5. One of skill

in the art would be motivated to increase the amount of C3bi on the surface of the bacteria in order to more efficiently target the bispecific or heterospecific antibodies of Fanger et al.

17. Applicant argues against the teachings of Fanger stating that Fanger describes anti-Fc receptor antibodies and bifunctional antibodies comprising at least one antigen binding region derived from an anti-Fc receptor, and at least one antigen-binding region specific from a target cell fro the use in the treatment of cancer, allergies, infectious and autoimmune diseases, and that Fanger does not teach, suggest or contemplate methods inhibiting or suppressing microbial replication in an animal comprising administering to said animal and anti-C3b(i) antibody. This has been considered but not found persuasive. The "antigen-binding region specific for a target cell" for use in the treatment of infectious diseases can be C3b or C3b(i) in light of the teachings of Newman regarding the presence of bound C3b and bound C3bi on the surface of free S pnemoniae, S pyrogenes, S aureus and H influenza when exposed to serum containing complement.

18. Claims 54-62 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

19. All other rejections or objections as set forth in the previous Office action are withdrawn in light of applicant's amendments.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
11/28/2005

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PRIMARY EXAMINER